Interim Analysis For Normally Distributed Observables

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We address the problem of whether an experiment should be continued or aborted when N observations are in hand and a total of S > N have been scheduled for a decision. A Bayesian predictive approach is used to determine the probability that if one continued the trial with a further sample of size M where $N+M \geq S$ one would come to a particular decision regarding some set of parameters. In particular, sampling from a multivariate normal distribution will be discussed.

1. Introduction

Often experiments will consist of a series of independent observations with some minimum sample size, say K, required before a conclusion is reached concerning the efficacy of a new treatment. Many such trials are costly and time consuming. Frequently an investigator would like to know at some interim point whether the continuation of the trial is worthwhile. With regard to a new treatment or a therapy, the issue is invariably whether continuation will lead to a conclusion that the treatment is at least as effective as some standard. There are frequentist methods which control type I and type II errors if interim analyses are made at preset sample sizes in a sequential trial. Depending on the number of such interim analyses, the required sample difference can be much larger than in a trial where no interim analyses are made. Also it is not always convenient to conduct such analyses at preset sample sizes in a trial. Other methods that allow for analyses at arbitrary sample sizes involve highly conservative tests which render even more difficult the detection of differences.

Although Bayesian statisticians do not suffer from such restrictions they may also be subject to an important trial which requires at least some fixed number of observations before a conclusion is reached. This is particularly true if the conclusion is to be convincing to a wider public or in particular to a regulatory agency which licenses new therapies. Hence Bayesians also need to consider interim analyses in order to decide whether to abandon a trial or to continue a trial to its specified term.

2. A Mixed Metaphor

In the last few years some Bayesian procedures have been suggested for those who prefer a frequentist analysis, Choi and Pepple (1989), Choi et al. (1985) and Spiegelhalter et al. (1986). First we shall illustrate the procedures suggested in a very simple case and indicate certain difficulties that arise if they are used.

Suppose $X_1,\ldots,X_{N+M}$ are i.i.d. $N(\mu,1)$ and a test of the following hypotheses is required, H_0: $\mu \le \mu_0$ vs. H_1: $\mu > \mu_0$. The standard test for testing H_0 vs. H_1 at level α is to reject H_0 if

$$\sqrt{N+M}\,(\bar{x}_{N+M}-\mu_0) > z_\alpha \tag{2.1}$$

where $\alpha = 1-\Phi(z_\alpha)$, and $\Phi(\cdot)$ is the standard normal distribution function.

To conduct an interim analysis at N observations, it is suggested that the probability of achieving the above event (2.1) be calculated. A syncretic approach has been proposed and developed in the previously mentioned papers which apply Bayesian predictive ideas towards the solution of this problem. It is assumed that the prior for μ is constant to conform as closely as possible to a frequentist analysis. After N observations are in hand, this results in a posterior distribution for μ as $N\left(\bar{x}_N, \frac{1}{N}\right)$. Now we compute the probability of the rejection set in (2.1)

$$\Pr\left[(N+M)^{1/2}\left[\frac{N\bar{x}_N + M\bar{X}_M}{N+M} - \mu_o\right] > z_\alpha \right] = P_\alpha \tag{2.2}$$

noting that now $\bar{x}_N$ is fixed but the as yet unobserved $\bar{X}_M$ is random. The predictive distribution of $\bar{X}_M$ is easily obtained to be $N\left(\bar{x}_N, \frac{1}{N}+\frac{1}{M}\right)$. Regrouping terms in (2.2) and letting

$$Z = (\bar{X}_M - \bar{x}_N) \Big/ \left(\frac{1}{N}+\frac{1}{M}\right)^{1/2}$$

we obtain

$$P_\alpha = \Pr\left[Z \geq \frac{z_\alpha\sqrt{N+M} - (M+N)(\bar{x}_N - \mu_o)}{M\sqrt{\frac{M+N}{MN}}} \right]$$

where Z is N(0,1). Finally, this yields

$$P_\alpha = 1 - \Phi\left(\left(\frac{N}{M}\right)^{1/2}[z_\alpha - (M+N)^{1/2}(\bar{x}_N - \mu_o)]\right), \tag{2.3}$$

the probability that if the trial were continued for an additional M observations, H_0 would be rejected at level α. Small values of P_α would discourage while large values would encourage the continuation of the trial . It follows from (2.3) that

$$\lim_{M \to \infty} P_\alpha = 1 - \Phi(-\sqrt{N}\,(\bar{x}_N - \mu_o)) = 1 - P \tag{2.4}$$

where

$$P = \Pr[Z \geq \sqrt{N}\,(\bar{x}_N - \mu_o)],$$

the P-value at N observations for testing H_0 which is independent of α. The limiting result of (2.4) turns out to be the posterior probability of the alternative as is indicated subsequently in (3.2).

This implies that if one continued the trial indefinitely, the predictive probability of rejecting H_o approaches 1–P irrespective of α. This is a "Bayesian" interpretation of 1–P that naïve students and some investigators often make with regard to significance tests. Further, teachers of frequentist statistics often strive mightily to disabuse students of this flawed interpretation. The result does not have an acceptable frequentist interpretation and furthermore, this is not the kind of test a Bayesian would apply. Hence one needs to be rather careful in mixing metaphors.

3. The Bayes Approach

A Bayesian approach in this situation would reject H_0, say, if the posterior probability, for a specified p, is

$$\Pr[\mu > \mu_o \mid x_1, \ldots, x_{N+M}] \geq p$$

assuming a prior $\pi(\mu)$ for μ. Hence, after N observations one would calculate the predictive probability of the above event assuming $x_1, \ldots, x_N$ have been observed and future observables $X_{N+1}, \ldots, X_{N+M}$ are random. In this example if the previous prior for μ is used, then $\mu \sim N\left(\bar{x}_{N+M}, \frac{1}{N+M}\right)$. Hence H_o is rejected if

$$\Pr[\sqrt{N+M}\,(\mu-\bar{x}) > \sqrt{N+M}\,(\mu_0-\bar{x})] \geq p$$

or

$$1-\Phi(\sqrt{N+M}\,(\mu_0-\bar{x})) \geq p,.$$

where $(N+M)\bar{x} = x_1 + \ldots + x_{N+M}$. Now stopping at N, we need to find the predictive probability of the above event i.e.

$$P_p = \Pr\left[1-\Phi\left(\sqrt{N+M}\left(\mu_o - \frac{N\bar{x}_N + M\bar{X}_M}{N+M}\right)\right) \geq p\right].$$

After some algebra, and denoting $\Phi^{-1}(p)$ as the inverse distribution function,

$$P_p = 1-\Phi\left(\left(\frac{N}{M}\right)^{1/2}\left[(\mu_o-\bar{x}_N)(N+M)^{1/2} - \Phi^{-1}(1-p)\right]\right) \tag{3.1}$$

is the chance of rejecting H_0 if the trial were continued.

Now if the trial were contemplated to be continued indefinitely,

$$\lim_{M\to\infty} P_p = 1-\Phi((\mu_o-\bar{x}_N)\sqrt{N}\,) = \Pr[\mu > \mu_o \mid x_1,\ldots,x_N] \tag{3.2}$$

which does not depend on p and is obviously the posterior probability given N observations. This is perfectly sensible as the best prediction of what would occur if one were to continue sampling indefinitely.

4. Normal Sampling with Mean and Variance Unknown

Let X_i, $i=1,\ldots,N+M$ be i.i.d. $N(\mu,\sigma^2)$ and $\pi(\mu,\sigma^2) \propto 1/\sigma^2$. Hence it is well known that

$$\frac{(\mu-\bar{x}_{N+M})\sqrt{N+M}}{S_{N+M}} \sim t_v$$

where t_v is a Student random variable with $v = N+M-1$ degrees of freedom. To test

$$H_0: \mu \leq \mu_0 \quad \text{vs.} \quad \mu > \mu_0,$$

we will decide for H_0 if the posterior probability

$$\Pr\left[\mu \leq \mu_0 \mid x^{(N+M)}\right] = S_v\left[\frac{(\mu_0-\bar{x}_{N+M})\sqrt{N+M}}{s_{N+M}}\right] \geq p,$$

$$(N+M)\bar{x}_{N+M} = \sum_{i=1}^{N+M} x_i,\ vs^2_{N+M} = \sum_{i=1}^{N+M} (x_i-\bar{x}_{N+M})^2$$

and $S_v(\bullet)$ is the Student distribution function with v degrees of freedom. After observing $x^{(N)}$ and some algebraic manipulation we find that we need to calculate

$$P_p = \Pr\left(\frac{\left[\mu_0-\frac{N\bar{x}_N}{N+M}-\frac{MX}{N+M}\right](N+M)^{1/2}(N+M-1)^{1/2}}{\left(z+Y+\frac{NM}{N+M}(X-\bar{x}_N)^2\right)^{1/2}} \geq S_v^{-1}(p)\right) \tag{4.1}$$

for $X = M^{-1}\sum_{i=N+1}^{N+M} X_i$, $z = (N-1)s_N^2 = \sum_{i=1}^{N}(x_i-\bar{x}_N)^2$, $Y = (M-1)s_M^2 = \sum_{i=N+1}^{N+M}(X_i-\bar{X}_M)^2$, and $S_v^{-1}(p)$ is the inverse student distribution function or the quantile function, where X and Y are the as yet unobserved random quantities. This requires the calculation of the joint predictive distribution of X and Y. This can easily be obtained, Geisser (1992), as

$$f(x,y|x^{(N)}) = \frac{\sqrt{MN}\,\Gamma\left(\frac{M+N-1}{2}\right) z^{\frac{N-1}{2}} y^{\frac{M-3}{2}}}{\sqrt{M+N}\,\Gamma\left(\frac{1}{2}\right)\Gamma\left(\frac{N-1}{2}\right)\Gamma\left(\frac{M-1}{2}\right)} \bullet \left[z+y+\frac{NM}{N+M}(x-\bar{x}_N)^2\right]^{-\frac{M+N-1}{2}},$$

where $x^{(N)} = (x_1,\ldots,x_N)$.

However, the distribution of the function of X and Y within the parentheses on the left-hand-side of the greater than or equal sign in (4.1) is fairly complex and is not readily tabled. Hence as a reasonable approximation for P_p for sufficiently large N, we shall approximate s_{N+M}^2 by known s_N^2 so that

$$S_v\left(\frac{(\mu_o-\bar{x}_{N+M})\sqrt{N+M}}{s_N}\right) \doteq S_v\left(\frac{(\mu_o-\bar{x}_{N+M})\sqrt{N+M}}{s_{N+M}}\right).$$

Then calculate

$$P_p \doteq \Pr\left(\frac{(\mu_o-\bar{x}_{N+M})\sqrt{N+M}}{s_N} \geq S_v^{-1}(p)\right)$$

$$\doteq \Pr\left(\frac{(\mu_o-\bar{x}_N)\sqrt{N+M} + (\bar{x}_N-X)\frac{M}{\sqrt{N+M}}}{s_N} \geq S_v^{-1}(p)\right)$$

$$\doteq 1 - S_{N-1}\left(\left(\frac{N}{M}\right)^{1/2}\left(S_v^{-1}(p) + \frac{(N+M)^{1/2}(\bar{x}_N-\mu_o)}{s_N}\right)\right).$$

This should serve as an adequate approximation for $N \geq 25$, until computing algorithms of the distribution function involved in (4.1) can be easily managed.

5. Multivariate Normal Observables

Let X_i be d-dimensional and i.i.d. $N(\mu,\Sigma)$, $i=1,2,\dots,n$. Suppose for some d-dimensional region R_o^d

$$H_0\colon \mu \in R_o^d \text{ vs. } H_1\colon \mu \notin R_o^d,$$

and we reject H_o if at $n = N+M$ obs.

$$\Pr[\mu \notin R_o^d \mid x^{(n)}] \geq p \tag{5.1}$$

for $x^{(n)} = (x_1,\dots,x_n)$. Assuming $p(\mu,\Sigma^{-1}) \propto |\Sigma|^{(d+1)/2}$ and $(n-1)S_n = \sum_{i=1}^{n} (x_i-\bar{x}_n)(x_i-\bar{x}_n)'$, we obtain that the posterior distribution of $\mu \sim S\left(n-d,\bar{x}_n,\frac{(n-1)}{n} S_n\right)$, i.e. a d-variate student distribution whose density is defined as

$$f(x) \propto (1 + (x-\theta)'\Lambda^{-1}(x-\theta))^{-\frac{\alpha+d}{2}}$$

so that $X \sim S(\alpha,\theta,\Lambda)$, Geisser and Cornfield (1963). Stopping at N we need to compute

$$\Pr[\Pr[(\mu \notin R_o^d \mid x^{(N)}, X_{(M)}] \geq p]$$

where $X_{(M)} = (X_{N+1},\dots,X_{N+M})$ is now random. Now

$$\Pr[\mu \notin R_o^d \mid x^{(N)}, X_{(M)}] = U(X_{(M)} \mid x^{(N)})$$

is a scalar random variable so that we are required to find

$$\Pr[U \geq p] = P_p.$$

An important application is when R_o^d is a hyperrectangle or semi-infinite hyperrectangle. Here simulation appears to be the simplest method of calculating P_p if the dimension d is small.

Another particular application which may be of some interest is the "distance" between two populations or the "distance" of a population from some specified d-dimensional vector say μ_o. Let γ be the distance of the population from μ_o so that

$$\gamma = (\mu-\mu_o)'\Sigma^{-1}(\mu-\mu_o).$$

Interest can focus on whether this normed difference of μ from some μ_o is less than some given distance. A similar situation can be defined for two populations. Further suppose we are interested in testing H_0: $\gamma \leq \gamma_o$ vs. H_1: $\gamma > \gamma_o$. Now for $n = N+M$ observations and Σ known, $n\gamma \sim \chi_d^2(\lambda)$ where $\lambda = n(\bar{x}_n-\mu_o)'\Sigma^{-1}(\bar{x}_n-\mu_o)$. Further $\frac{\nu\lambda}{T^2} \sim \chi_\nu^2$ for $\Sigma^{-1} \sim W(\nu,\nu^{-1}S_n^{-1})$ i.e. Wishart distributed, for $\nu = n-1, \nu S_n = \sum_{i=1}^{n}(x_i-\bar{x}_n)(x_i-\bar{x}_n)'$, and

$$T^2 = n(\bar{x}_n-\mu_o)'S_n^{-1}(\bar{x}_n-\mu_o).$$

Now we can find the posterior density,

$$p_{T^2}(\gamma \mid x^{(n)}) = \int p(\gamma|\lambda,x^{(n)})p_{T^2}(\lambda|x^{(n)})\,d\lambda$$

and it is possible to show that

$$p_{T^2}(n\gamma \mid x^{(n)}) = \sum_{j=0}^{\infty} w_j \, f_{d+2j}(n\gamma)$$

where $f_{d+2j}(n\gamma)$ is the density of a chi-squared random variable with d+2j degrees of freedom and

$$w_j = \binom{\frac{\nu}{2}+j-1}{j} \left(\frac{\nu}{T^2+\nu}\right)^{\frac{\nu}{2}} \left(\frac{T^2}{T^2+\nu}\right)^{j},$$

Geisser (1967).

Note that as n grows,

$$w_j \rightarrow \left(\frac{T^2}{2}\right)^{j} \frac{e^{-\frac{T^2}{2}}}{j!}.$$

Hence $n\gamma$ will tend to a non-central chi-squared variate with d degrees of freedom and non-centrality parameter T^2.

To reject H_0 we require $\Pr[n\gamma > n\gamma_0 \mid x^{(N+M)}] \geq p$ or $1 - F_{T^2}(n\gamma_0) \geq p$. Now if we stop at N we need to calculate $P_p = \Pr[1 - F_{T^2}(n\gamma_0) \geq p]$ for n = N+M. Because we can show that $1 - F_{T^2}((N+M)\gamma_0)$ is increasing in T^2, we need to find the minimum T^2, say t_0^2, such that

$$1 - F_{t_0^2}((N+M)\gamma_0 \geq p$$

and then

$$P_p = \Pr(T^2 > t_o^2).$$

To demonstrate the monotonicity property we note that

$$1 - F_{T^2}(y) = \Pr(n\gamma > y)$$
$$= \sum_{j=0}^{\infty} w_j \, G_{d+2j}(y)$$

where G_{d+2j} is the distribution function corresponding to $f_{d+2j}(n\gamma)$. Define

$$c_j = \binom{\frac{\nu}{2}+j-1}{j}, \quad \eta = \left(\frac{T^2}{T^2+\nu}\right)$$

then it suffices to establish monotonicity in η. Now it is easy to show that

$$\frac{dw_j}{d\eta} = \left(\frac{\nu}{2}+j-1\right) w_{j-1} - \frac{\nu}{2}(1-\eta)^{-1} w_j$$

so that after some algebraic manipulation

$$\frac{d}{d\eta}[1 - F_{T^2}(y)] \propto \sum_{j=0}^{\infty} w_j(G_{d+2+2j}(y) - G_{d+2j}(y)) + \sum_{j=0}^{\infty} w_j \frac{(2j-T^2)}{\nu+T^2} G_{d+2+2j}(y). \qquad (6.1)$$

Now we show that for any integer k

$$G_{k+2}(y) > G_k(y) \qquad (6.2)$$

which implies that the first term in (6.1) is non-negative. Let

$$G_{k+2}(y) - G_k(y) = h(y) = \int_y^\infty \left(\frac{x}{k} - 1\right) f_r(x)\, dx.$$

Clearly $h(y) > 0$ if $y > k$. Furthermore,

$$\frac{dh(y)}{dy} = -\left(\frac{y}{k} - 1\right) f_k(y) > 0$$

if and only if $y < r$. Thus $h(y)$ is monotonically increasing for $y \leq k$ and then monotonically decreasing. Because $h(0) = 0$ it then follows that $h(y) > 0$ for all $0 < y < k$ and (6.2) is established. Hence the first term in (6.1) is positive for $y > 0$.

We now consider the second term in (6.1). Define $g(\bullet)$ to be a differentiable increasing version of $G_{d+2j}(y)$ so that $g(c)$ is differentiable, increasing and $g(c) = G_{d+2j}(y)$ provided that $c = j$. Then the second term of (6.1) is proportional to

$$\sum_{j=0}^{\infty} w_j\left(j - \frac{T^2}{2}\right)g(j). \tag{6.3}$$

A first order Taylor expansion about $\frac{T^2}{2}$ yields

$$g(j) = g\left(\frac{T^2}{2}\right) + g'(j^*)\left(j - \frac{T^2}{2}\right)$$

for $j^* \in \left(j, \frac{T^2}{2}\right)$. Expression (6.3) then becomes

$$g\left(\frac{T^2}{2}\right) \sum_{j=0}^{\infty} w_j\left(j - \frac{T^2}{2}\right) + \sum_{j=0}^{\infty} w_j g'(j^*)\left(j - \frac{T^2}{2}\right)^2.$$

But $g'(j^*) > 0$ and

$$\sum_{j=0}^{\infty} j\, w_j = \frac{T^2}{2}\,.$$

Hence the second term in (6.1) is also positive and the monotonicity property is established.

6. An Approximation to the Predictive Distribution of T^2

Now T^2 depends on the random variables $\bar{X}_M$ and S_M since

$$T^2 = (N+M)\left(\frac{N\bar{x}_N+M\bar{X}_M}{N+M} - \mu_o\right)' S_{N+M}^{-1} \left(\frac{N\bar{x}_N+M\bar{X}_M}{N+M} - \mu_o\right)$$

where

$$(N+M-1)S_{N+M} = (N-1)S_N + (M-1)S_M + \frac{NM}{M+N}(\bar{X}_M - \bar{x}_N)(\bar{X}_M - \bar{x}_N)'.$$

The joint predictive density of $\bar{X}_M = X$ and $(M-1)S_M = Y$ is easily found to be

$$f(x,y|x^{(N)}) \propto |y|^{\frac{M-d-2}{2}} \left|\frac{NM}{N+M}(x-\bar{x}_N)(x-\bar{x}_N)' + y + z\right|^{-\frac{N+M-1}{2}},$$

for $z = (N-1)S_N$. However, the calculation of the exact density of T^2 is even less tractable from the above than in the univariate case i.e. $d = 1$, discussed in section 4.

Define

$$V = \frac{N\bar{x}_N+M\bar{X}_M}{N+M},$$

so that

$$T^2 = (N+M)(V-\mu_o)'S_{N+M}^{-1}(V-\mu_o).$$

As in the univariate case we will approximate S_{N+M} by S_N thus eliminating the random matrix S_M and alter T^2 to

$$\hat{T}^2 = (N+M)(V-\mu_o)'S_N^{-1}(V-\mu_o)$$

and derive the density of $\hat{T}^2$. Define $Q = \frac{M}{N(N+M)} S_N$, $q = N - d$. Then

$$V - \bar{x}_N \sim S(q,0,(N-1)Q).$$

Now given $x^{(N)}$ consider the random vector $W(\frac{q}{U})^{1/2}$, where W is N(0,Q) and independent of U which is $\chi^2_{N\text{-}d}$. Let $\delta = \bar{x}_N - \mu_o$. Then the vector $V - \mu_o$ is distributed as $W(\frac{q}{U})^{1/2} + \delta$. Hence $\hat{T}^2$ is distributed as

$$(N+M)\left(W + \left(\frac{U}{q}\right)^{1/2}\delta\right)' S_N^{-1}\left(W + \left(\frac{U}{q}\right)^{1/2}\delta\right)\left(\frac{q}{U}\right)^{1/2}.$$

Conditional on U, $W + \left(\frac{U}{q}\right)^{1/2}\delta \sim N\left(\left(\frac{U}{q}\right)^{1/2}\delta, Q\right)$ so that

$$\left(W + \left(\frac{U}{q}\right)^{1/2}\delta\right)'Q^{-1}\left(W + \left(\frac{U}{q}\right)^{1/2}\delta\right) \sim \chi^2_p\left(\frac{\delta'Q^{-1}\delta U}{q}\right)$$

i.e. non-central chi-square with d degrees of freedom and non-centrality parameter

$$\delta'Q^{-1}\delta U/q \equiv DU.$$

Thus conditional on U

$$\frac{N}{Mq}\hat{T}^2 \sim \chi_d^2(DU)/U.$$

The predictive density of $\frac{N}{Mq}\hat{T}^2 = A$ is then

$$f(a|x^{(N)}) = \int_0^\infty f_U(u|x^{(N)})\, f(ua|x^{(N)},u)\, udu$$

$$= \sum_{k=0}^{\infty} \frac{\Gamma(2k+\frac{N}{2})}{k!\,\Gamma(k+\frac{d}{2})\,\Gamma(\frac{q}{2})} \left(\frac{D}{1+D}\right)^k \left(\frac{1}{1+D}\right)^{k+\frac{N}{2}} a^{k+\frac{d}{2}-1}\left(1+\frac{a}{1+D}\right)^{-(2k+\frac{N}{2})} \tag{5.1}$$

From (5.1) it is clear that $A(1+D)^{-1} = B$ has density

$$f(b|x^{(N)}) = \sum_{k=0}^{\infty} w_k\, f(b|k+\tfrac{d}{2},\, k+\tfrac{q}{2}),$$

an infinite sum of beta variates, i.e.

$$f\left(b \mid k+\frac{d}{2},\, k+\frac{q}{2}\right) \propto b^{k+\frac{d}{2}-1}(1+b)^{-(2k+\frac{d+q}{2})} \tag{5.2}$$

with negative binomial weights, where

$$w_k = \binom{k+\frac{q}{2}-1}{k}\left(\frac{D}{1+D}\right)^k\left(\frac{1}{1+D}\right)^{q/2}.$$

Hence

$$B = \frac{N\hat{T}^2}{M(N-p)(1+D)}$$

so that

$$P_p = \Pr(T^2 > t_o^2) \doteq \Pr(\hat{T}^2 > t_o^2) = \Pr\left(B > \frac{Nt_o^2}{M(N-p)(1+D)}\right)$$

which can be numerically calculated to reasonable accuracy.

We have provided an approximation for the solution of this problem that can be numerically calculated. The question now is how good this approximation is with regard to the exact P_p. The approximation will obviously improve as N increases for any given d. Some simulation work would be necessary to ascertain the values N must exceed to attain given bounds on approximation error for various values of d.

7. Remarks

As noted before, this work can be adapted to the two population problem. However, the case of k populations presents further complications and will be the scope of further work including interim analysis in multivariate normal classification problems.

References

Choi, S.C. and Pepple, P.A. (1989). Monitoring clinical trials based on predictive probability of significance. Biometrics 45, 317-323.

Choi, S.C., Smith, P.J. and Becker, D.P. (1985). Early decision in clinical trials when treatment differences are small. Controlled Clinical Trials 6, 280-288.

Geisser, S. (1967). Estimation associated with linear discriminants. Annals of Mathematical Statistics 38, 3, 807-817.

Geisser, S. (1992). On the curtailment of sampling. Canadian Journal of Statistics (in press).

Geisser, S. and Cornfield, J. (1963). Posterior distributions for multivariate normal parameters. Journal of the Royal Statistical Society B, 25, 368-376.

Spiegelhalter, D.J., Freedman, D.S., and Blackburn, P.R. (1986). Monitoring clinical trials: Conditional or predictive power? Controlled Clinical Trials 7, 8-17.